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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,176	09/02/2005	Klaus Sommermeyer	3675.1001-0000	8000

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EXAMINER	
GOON, SCARLETT Y	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,176	SOMMERMEYER, KLAUS	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-68* is/are pending in the application.

4a) Of the above claim(s) *54-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *35-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicants' Amendment and Remarks filed on 13 April 2009 in which claims 1-34 were previously cancelled, claims 35, 36, 40, 41, 42, 47, 49-52, 54, 55, 58, 59 and 68 are amended to change the scope and breadth of the claims, and claims 37-39 and 45 are amended to correct for typographical and grammatical matters.

Claims 35-68 are pending in the instant application.

Claims 54-68 were previously withdrawn from further consideration in the Office Action dated 8 December 2008 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or nonelected species, there being no allowable generic or linking claim.

Claims 35-53 are examined on its merits herein.

Priority

This application is a National Stage entry of PCT/EP03/13622 filed on 3 December 2003 and claims priority to Germany foreign application 10256558.9 filed on 4 December 2002. A certified copy of the foreign priority document in German has been received. No English translation has been received.

Rejections Withdrawn

Applicant's amendment and arguments, filed 13 April 2009, with respect to the rejection of claims 35-53 under 35 USC § 112, second paragraph, as being indefinite by

reciting "derivative," have been fully considered and is persuasive because the amended claims no longer recite the phrase "derivative."

Applicant's amendment and arguments, filed 13 April 2009, with respect to the rejection of claim 38 under 35 USC § 112, second paragraph, as being indefinite by reciting "in the range of greater than 10 to 25 mol %," have been fully considered and is persuasive because the amended claims deletes the phrase "greater than."

Applicant's amendment and arguments, filed 13 April 2009, with respect to the rejection of claims 39, 40 and 42 under 35 USC § 112, second paragraph, as being indefinite by reciting "MW," have been fully considered and is persuasive because the amended claims places the recitation "MW" within parentheses to indicate that it is an abbreviation for molecular weight.

Applicant's amendment and arguments, filed 13 April 2009, with respect to the rejection of claim 42 under 35 USC § 112, second paragraph, as being indefinite by reciting "MS," have been fully considered and is persuasive because the amended claim indicates that "MS" is an abbreviation for "molar substitution."

Applicant's amendment and arguments, filed 13 April 2009, with respect to the rejection of claim 47 under 35 USC § 112, second paragraph, as being indefinite by reciting "N-hydroxysuccinimide and sulfo-N-hydroxysuccinimide," have been fully considered and is persuasive because the amended claims corrects the recitation to "N-hydroxysuccinimide or sulfo-N-hydroxysuccinimide."

Applicant's amendment and arguments, filed 13 April 2009, with respect to the rejection of claims 35-38, 41, 43-46 and 49 under 35 USC § 102(b), as being

anticipated by WIPO publication WO 2002/080979 by Sommermeyer *et al.*, have been fully considered and is persuasive because the teachings of Sommermeyer *et al.* do not anticipate the claim limitations of an isolated aldonic acid ester, as instantly claimed.

Applicant's amendment and arguments, filed 13 April 2009, with respect to the rejection of claims 39, 40 and 42 under 35 USC § 103(a), as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.* as applied to claims 35-38, 41, 43-46 and 49, have been fully considered and is persuasive because the teachings of Sommermeyer *et al.* do not teach the amended claim limitations of an isolated aldonic acid ester.

These rejections have been **withdrawn**.

The following are new ground(s) or modified rejections necessitated by Applicants' amendment, filed on 13 April 2009, wherein the limitations in pending claim 35 as amended now have been changed; claims 36-53 depend from claim 35. The limitations in the amended claims have been changed and the breadth and scope of those claims have been changed. Therefore, the rejections from the previous Office Action, dated 8 December 2008, have been modified and are listed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "optionally substituted polysaccharide" in claims 35, 36 and 41 render the claims herein indefinite. In the absence of further indicating what the optional substitutes are that can be used to substitute the polysaccharide, one would not be apprised of the metes and bounds of what Applicants intend to claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Section [0001]

Claims 35-38 and 41-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.* (IDS dated 26 June 2008, PG Pub No. US 2005/0063943 A1 used as English equivalent translation), in view of chapter entitled "Zero-Length Cross-linkers" by Hermanson (of record), as evidenced by Marder *et al.* (of record), and as evidenced by "WHO Food Additives Series No. 5" (of record).

Sommermeyer *et al.* teach compounds comprising a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyl alkyl starch is coupled to the active ingredient either directly or via a linker (paragraph 0029). HAS is preferably oxidized at the reducing end prior to binding to the active ingredient (paragraph 0031). Hydroxyethyl starch (HES) is the preferred HAS (paragraph 0050). HES is a substituted derivative of the carbohydrate polymer amylopectin which occurs in maize starch in a concentration of up to 95% (paragraph 0019). Any physiologically compatible HES can be used as the starting material, although HES with an average molecular weight of 2 to 40 kD is preferred (paragraph 0134). HES preferably has a molar degree of substitution of 0.1 to 0.8 and a ratio of C_2:C_6 substitution in the range of 2 to 20 (paragraph 0134). When HAS is bound to the active ingredient via a linker, the linker may be an amino acid, hydrazine or oxylamine derivative, among others (paragraph 0126).

Sommermeyer *et al.* disclose in Example 2 (paragraph 0147) a compound wherein hydroxyethyl starch oxidized at the reducing end is reacted with HSA in the presence of EDC, in water. This is further exemplified in Table 2 (p. 11). Although not explicitly indicated by Sommermeyer *et al.*, it is evidenced by Marder *et al.* that when an acid (i.e. oxidized hydroxyethyl starch) is reacted with EDC, an O-acylisourea intermediate, containing an ester linkage (compound (1) of Figure 1), is formed. When this reaction takes place in the presence of HOBt, a different ester (as defined by Applicant on p. 9 of the Specification) is formed, that between the acid and the hydroxyl group of HOBt (see compound (5) in Figure 1).

It is noted that Sommermeyer *et al.* do not explicitly indicate that HES used is the conjugation is amylopectin degradation fractions. However, as evidenced by the article entitled "WHO Food Additives Series No. 5" (of record), the molecular weight of waxy corn starch can be as high as 80,000,000. Therefore, since Sommermeyer *et al.* disclose that HES is a substituted derivative of the carbohydrate polymer amylopectin which occurs in maize starch (paragraph 0019) and preferably uses HES with an average molecular weight of 2 to 40 kD is preferred (paragraph 0134), it is the Office's position that the HES described by Sommermeyer *et al.* is derived from amylopectin degradation fractions to obtain HES with an average molecular weight of 2 to 40 kD.

Although Sommermeyer *et al.* teach the activation of HES with EDC/HOBt prior to conjugation with HSA, Sommermeyer *et al.* do not teach that this activated ester intermediate is, or can be, isolated.

Hermanson teaches that EDC, a popular carbodiimide used in conjugation of biological substances, is labile in the presence of water (p. 170, section 1.1, paragraph 1). In the aqueous solutions, the oxygen atom of water can act as a nucloephile. Thus, hydrolysis of the O-acylisourea intermediate is a major competing reaction (p. 170, section 1.1, paragraph 2). An alternative is to use EDC in the presence of sulfo-N-hydroxysuccinimide (sulfo-NHS). Forming a sulfo-NHS ester intermediate from the reaction of the hydroxyl group on sulfo-NHS with the EDC active-ester complex extends the half-life of the activate carboxylate group to hours (p. 173, section 1.2, paragraph 2). Furthermore, EDC/sulfo-NHS-coupled reactions are highly efficient and usually increase the yield of conjugation dramatically over that obtainable solely with EDC (p. 173,

section 1.3, paragraph 3). A protein can be incubated in the presence of EDC/sulfo-NHS and the active ester form can be isolated. The isolated active ester is then mixed with a second protein or other amine-containing molecule for conjugation (p. 173, last paragraph). This two step process allows the active species to form only on one protein, thus gaining greater control over the conjugation.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Sommermeyer *et al.*, concerning a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyalkyl starch is coupled to the active ingredient either directly or via a linker using EDC, with the teachings of Hermanson, regarding the use of EDC/sulfo-NHS in a conjugation reaction as an alternative to EDC. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Hermanson, that the reaction of the hydroxyl group on sulfo-NHS with the EDC active-ester complex extends the half-life of the activate carboxylate group to hours (p. 173, section 1.2, paragraph 2) and that this reaction usually increases the yield of conjugation dramatically over that obtainable solely with EDC (p. 173, section 1.3, paragraph 3). Furthermore, one would have been motivated to combine the teachings and modify the conjugation procedure taught by Sommermeyer *et al.* such that the activated ester intermediate of HES is isolated prior to conjugation with HSA, in order to receive the expected benefit, as suggested by Hermanson, that sulfo-NHS activated ester complexes can be isolated before conjugation to another compound, thereby permitting greater control over the conjugation as only one reaction can occur to form the desired product rather than the

formation of side products which can occur when intermediates are not isolated from their reaction conditions.

It is noted that the Sommermeyer *et al.* and Hermanson references do not teach a solution comprising the aldonic acid ester wherein the solution comprises not more than 0.5% by weight of water, or is an aprotic solvent. However, as Hermanson teaches that an EDC conjugate is labile in the presence of water and thus can undergo hydrolysis, it would have been *prima facie* obvious that one of ordinary skill in the art, a chemist, would have the aldonic acid ester in an aprotic organic solvent such as DMF or DMSO, rather than in water, so as to avoid hydrolysis of the aldonic acid ester. Although discussed with a different carbodiimide, this point is further illustrated by Hermanson in saying that "active ester synthesis done...in an organic solvent...does not have the hydrolysis problems of water-soluble EDC-formed ester" (p. 178). It is commonly known among chemists that DMF is a polar aprotic solvent used as a substitute for water when an aprotic organic solvent is desired.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0002]

Claims 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.* (IDS dated 26 June 2008, PG Pub No. US 2005/0063943 A1 used as English equivalent translation), in view of chapter entitled "Zero-Length Cross-linkers" by Hermanson (of record), as evidenced

by Marder *et al.* (of record), and as evidenced by "WHO Food Additives Series No. 5" (of record), as applied to claims 35-38 and 41-53, further in view of journal publication to Gunja *et al.* (PTO-892, Ref. U), in view of journal publication by Mua *et al.* (PTO-892, Ref. V).

The teachings of Sommermeyer *et al.*, Hermanson, Marder *et al.* and the publication by WHO were as disclosed in section [0001] above of the claim rejections under 35 USC § 103.

Sommermeyer *et al.* is silent with regards to the average branching of α-1,6-glycosidic linkages in the starch fractions.

Gunja *et al.* teach the enzymic conversion of amylopectin into glycogen-type polysaccharide. Table 2 shows that potato amylopectin has an average of 4-5% of α-1,6-glycosidic linkages (p. 1017, column 2). The introduction of the yeast branching enzyme further increases the branching by approximately 2-9% (p. 1017, column 2, last paragraph), resulting in a degree of branching of up to 14%.

Mua *et al.* teach the gel textural attributes of corn starch amylose and amylopectin fractions that vary in molecular weight and degree of branching. Starches isolated from different botanical sources have different functional properties and are used in foods and non-food products (p. 157, column 1). For amylopectin, the molecular structure and degree of branching govern the starches' gel textural properties (abstract). Highly branched amylopectins exhibit decreased ahdesive force and increased stringiness (p. 164, column 2). Knowing the relationships between the

molecular structure and functional attributes of the starch could pave the way for new and improved starch uses (p. 157, column 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Sommermeyer *et al.*, concerning a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyalkyl starch is coupled to the active ingredient either directly or via a linker using EDC, with the teachings of Hermanson, regarding the use of EDC/sulfo-NHS in a conjugation reaction as an alternative to EDC, with the teachings of Gunja, regarding the use of a yeast enzyme to increase the degree of branching in amylopectin from 4-5% up to 14%, with the teachings of Mua *et al.*, regarding the influence branching has on the gelling properties of amylopectin. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Mua *et al.*, that the degree of branching can be used to affect the gelling properties of amylopectin. Thus, it is considered *prima facie* obvious for one of ordinary skill in the art to choose an amylopectin, with the appropriate degree of branching to yield a product with the desired gelling properties, for conjugation to a drug.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's amendment and arguments filed 13 April 2009 with respect to the rejection of claims 47, 48 and 50-53 made under 35 USC § 103(a) as being

unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.*, in view of Hermanson, have been fully considered but are moot in view of the modified rejections above.

Applicants argue that the Sommermeyer *et al.* reference does not teach an isolated aldonic acid ester. Applicants further argue that because Hermanson likewise does not teach an isolated aldonic acid ester, Hermanson does not cure the deficiency of the Sommermeyer *et al.* reference. This argument is not persuasive because, as indicated in the rejections above, Hermanson specifically teaches that sulfo-NHS activated ester can be isolated in order to gain greater control in the conjugation step. Thus, one of ordinary skill in the art aware of Hermanson's teachings would modify the conjugation procedure taught by Sommermeyer *et al.* by first activating HES to an activated ester intermediate and isolating this intermediate prior to introducing HSA for conjugation.

Modified grounds of rejection for the currently amended claims, necessitated by Applicant's amendments, are as indicated above.

The rejection is still deemed proper and therefore adhered to.

Conclusion

In view of the rejections to the pending claims set forth above, no claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

SCARLETT GOON
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